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(54) **Use of L-2-oxo thiazolidine-4-carboxylate for the treatment of pulmonary diseases**

Verwendung von L-2-oxo Thiazolidin-4-carboxylat zur Behandlung von Atemnotsyndrom

Utilisation de L-2-oxo thiazolidine-4-carboxylate pour le traitement d'un syndrome de gêne respiratoire

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(56) References cited:

EP-A- 0 057 942 BE-A- 880 744

- **BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS**, vol. 127, no. 1, 28th February 1985, pages 270-276, Academic Press, Inc.; M.-F. TSAN et al.: "Enhancement of intracellular glutathione protects endothelial cells against oxidant damage"
- **INFLAMMATION**, vol. 12, no. 2, 1988, pages 113-121, Plenum Publishing Corp.; M.-F. TSAN et al.: "L-2-oxothiazolidine-4-carboxylate protects cultured endothelial cells against hyperoxia-induced injury"
- **AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY**, vol. 2, no. 1, January 1990, pages 81-90; P.H.S. SPORN et al.: "Complex effects of In Vitro hyperoxia on alveolar macrophage arachidonic acid metabolism"
- **AM. REV. RESPIR. DIS.**, vol. 133, 1986, page A395; M.A. PASSERO et al.: "L-2-oxothiazolidine-4-carboxylic acid increases glutathione in mouse lung"
- **BIOCHEMICAL PHARMACOLOGY**, vol. 39, no. 12, 1990, Pergamon Press plc, GB, pages 1877-1881; S. UHLIG et al.: "Glutathione enhancement in various mouse organs and protection by glutathione isopropyl ester against liver injury"
- **BIOCHEMICAL PHARMACOLOGY**, vol. 38, no. 22, pp. 3981-3985 (1989)
- **AM. REV. RESPIR. DIS.**, vol. 139 (4), p. A 221 (1989)

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Description**BACKGROUND OF THE INVENTION**

[0001] The present invention relates to the preparation of compositions that can be used for the treatment of diseases that result in acute and/or chronic respiratory distress, or for the treatment of respiratory distress syndrome.

[0002] There are a number of pulmonary or respiratory disease states and acute processes that can cause acute or chronic respiratory distress and result in damage to the lungs of the patient. Resulting damage can be debilitating to the patient and on occasion result in death.

[0003] Adult respiratory distress syndrome (ARDS) is a common medical emergency that is precipitated by a variety of disease states or acute processes that directly or indirectly injure the lungs. For example, ARDS can be precipitated by primary bacterial or viral pneumonias, aspiration of gastric contents, direct chest trauma, prolonged or profound shock, burns, near drowning, fat embolism, blood transfusions, cardio-pulmonary bypass, O₂ toxicity, or acute hemorrhagic pancreatitis. ARDS usually develops within twenty-four to forty-eight hours after initial injury or illness. It is believed that activated leukocytes and platelets accumulate in the capillaries, interstitium, and airspaces. They may release products including prostaglandins, toxic O₂ radicals, proteolytic enzymes, and other mediators that injure cells, promote fibrosis, and alter bronchomotor tone and vasoreactivity. See, The Merck Manual, Fifteenth Edition.

[0004] Injury to the pulmonary capillary endothelium and alveolar epithelium causes plasma and blood to leak into the interstitial and intra-alveolar spaces. Flooding of the alveolae and atelectasis results. Typically, within two or three days, a second phase of lung injury is characterized by bronchoalveolar inflation. Additionally, there is proliferation of epithelial and interstitial cells. Typically, in a third phase collagen accumulation may progress rapidly. This can result in severe interstitial fibrosis within two to three weeks. This pathological change, can lead to low lung compliance, pulmonary hypertension, decreased functional residual capacity, ventilation/perfusion maldistribution, and hypoxemia.

[0005] Unfortunately, the survival rate for severe ARDS is less than 50% with appropriate treatment. Although the mechanism of lung injury in adult respiratory distress syndrome is not certain, data from animal models and indirect evidence from studies in human beings has suggested that toxic oxygen metabolites produced by stimulated neutrophils are a possible agent of the alveolar injury. Baldwin, et al., Oxidant Activity In Expired Breath of Patients With Adult Respiratory Distress Syndrome, The Lancet, January 4, 1986, pages 11-13.

[0006] Because it has been hypothesized that oxygen free radicals released during endotoxemia may contribute to the lung injury of ARDS, the effect of intravenous n-acetylcysteine, a free radical scavenger, on the endotoxin induced model of ARDS in awake sheep has been investigated. Bernard, et al., Effect of N-acetylcysteine on the Pulmonary Response to Endotoxin in the Awake Sheep and Upon In Vitro Granulocyte Function, J. Clin. Invest., Vol. 73, pp 1772-84 (1984). The paper states that n-acetylcysteine inhibits granulocyte aggregation and scavenges free radicals in vitro. The paper postulates, therefore, that the beneficial effect of n-acetylcysteine in attenuating the pathophysiologic processes seen in the sheep model of the adult respiratory syndrome is due to its ability to scavenge oxygen free radicals in vivo.

[0007] Lucht, et al., Prevention of Release of Granulocyte Aggregants Into Sheep Lung Lymph Following Endotoxemia By Acetylcysteine, The American Journal of the Medical Sciences, Vol. 294 No. 3 (September 1987), discusses experiments wherein n-acetylcysteine was administered to sheep before endotoxin infusion. The paper concludes that endotoxemia causes the release from the lungs of substance(s) that activate granulocytes, and that this response is prevented by n-acetylcysteine, possibly as a result of the antioxidant properties of the drug.

[0008] Although, attention has focused on treating and/or curing ARDS, an effective treatment is still not available.

[0009] Infant respiratory distress syndrome, or IRDS, is a disorder primarily of prematurity, manifested clinically by respiratory distress and pathologically by pulmonary hyaline membrane disease and atelectasis. See Merck Manual, Fifteenth Edition. IRDS results from diffuse lung atelectasis due to a deficiency of pulmonary surfactants at birth. Due to pulmonary insufficiency, these neonates are placed in hyperoxic (95% O₂) environments. The inability to produce adequate amounts of glutathione exacerbates the oxidative stress and damage to the lungs. If untreated, IRDS can result in bronchopulmonary dysplasia, blindness, brain damage, multiple organ failure and death.

[0010] Other disease states, such as cystic fibrosis, idiopathic pulmonary fibrosis, and emphysema, also can result in lung damage due to cell damage from oxidation. The lungs are exposed to oxidative stress due to airborne oxidants and to hyperoxygen stress when respiratory treatment includes elevated oxygen (e.g., 95% O₂) treatment. Additionally, inflammatory cells, macrophages, neutrophils, and the like, secrete active oxygen species in the lungs.

SUMMARY OF THE INVENTION

[0011] The present invention relates to use of L-2-oxothiazolidine-4-carboxylate in the manufacture of a composition for treating a respiratory distress syndrome in a patient suffering from same.

[0012] It has been found, that by increasing glutathione levels within a cell, the pulmonary cells will experience

reduced damage when exposed to oxidative stress. Cells having depressed glutathione levels are susceptible to membrane lipid peroxidation, mitochondrial damage, and progressive fibrosis of lung tissue. However, turnover of glutathione and of endogenous antioxidants in pulmonary endothelium is very rapid. Relevant background art documents are Biochem. Biophys. Res. Commun. 127, 270-276 (1985), Inflammation 12, 113-121 (1988), Am. J. Resp. Cell & Mol. Biol. 2, 81-90 (1990), Am. Rev. Resp. Dis. 133, A 395 (1986) and Biochem. Pharmacol. 39, 1877-1881 (1990).

[0013] L-2-oxothiazolidine-4-carboxylate is utilized according to the invention to elevate tissue glutathione levels, these compositions being convertible intracellularly to glutathione.

[0014] The present invention provides for the use of the composition to treat adult respiratory distress syndrome or infant respiratory distress syndrome which result in oxidative stress that can damage the cells of the lung.

[0015] The composition may be administered parenterally, or enterally.

[0016] Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

[0017] L-2-oxothiazolidine-4-carboxylate is a non-cysteine composition and is distributed effectively in tissues of the patient. It is believed that the enzymes necessary for deacetylation of an acetylated compound such as n-acetylcysteine exist only in the kidney. Accordingly, a compound such as n-acetylcysteine must be metabolized to cysteine in the kidney then transported to the liver or peripheral cells. Therefore, such compounds may not be sufficiently distributed to the requisite tissues of the patient, i.e., the tissue of the lungs.

[0018] Furthermore, the composition is not itself an anti-oxidant. Although it may be desirable to introduce an anti-oxidant into a patient having adult respiratory distress syndrome to prevent damage from the oxygen radicals, anti-oxidants are not stable.

[0019] L-2-oxothiazolidine-4-carboxylate, in vitro, is subjected to the action of 5-oxo-L-prolinase in the presence of adenosine triphosphate to produce S-carboxyl cysteine. S-carboxyl cysteine is then decarboxylated to produce cysteine. Cysteine is then metabolized to provide glutathione. See, U.S. Patent Nos.: 4,335,210; 4,434,158; 4,438,124; 4,665,082; and 4,647,571.

[0020] In an embodiment of the invention, the composition of the present invention includes: 3% L-2-oxothiazolidine-4-carboxylate (OTC) in a phosphate buffer. Additional embodiments include:

- a) A buffered (pH 6.5 - 6.8) 3% or 6% OTC aqueous solution.
- b) A buffered 3% or 6% OTC aqueous solution containing any of the following, alone or in appropriate combinations: amino acids, dextrose or other carbohydrate sources, and lipid emulsions.
- c) A vial containing a crystalline or lyophilized non-cysteine glutathione precursor to which appropriate aqueous solutions are added at time of use.
- d) A gelatin capsule containing a crystalline or lyophilized non-cysteine glutathione precursor.
- e) A pill containing a crystalline or lyophilized non-cysteine glutathione precursor.
- f) A liquid elemental, protein hydrolysate, carbohydrate and/or lipid emulsion containing enteral dietary supplement containing a non-cysteine glutathione precursor.

[0021] The composition can be administered as an adjunct therapy with other typical therapies. For example, steroids, non-steroid anti-inflammatories, prostaglandin synthesis inhibitors (ibuprofen), mucolytics, tumor necrosis factor antibodies, artificial surfactants (Exosurf, Surfactant), hyperoxic and ventilation therapies, and antibiotics can be administered with the present invention.

[0022] By way of example, but not limitation, contemplated examples of the present invention will now be given.

EXAMPLE 1

[0023] A 55-year-old patient with sepsis syndrome that progressed into ARDS was given an intravenous administration of a neutral (pH 6.5 - 6.8) 6% solution of L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d. for 10 days. It should be noted that a continuous infusion of a 6% solution equivalent to 45 mg/kg/day could have been used as an alternative dosing regimen. The infusion although by independent intravenous administration, could have been through an indwelling intravenous catheter.

[0024] The patient demonstrated the following physiological characteristics at the start and end of treatment:

Physiology	Start	End
PaO ₂ /PAO ₂	0.24	0.38
Cardiac Output (liters/min)	5.65	7.93
Thoracic Static Compliance (ml/cm H ₂ O)	34.4	42.3
Chest Radiograph of Pulmonary Edema (0 = normal, 3 = severe)	2.5	1.1
Plasma Glutathione (nmoles/ml)	2.47	7.96
Red Cell Glutathione (nmoles/ml)	2,753	5,825
Lung Glutathione (nmoles/ml by Bronchoalveolar lavage)	84	398

EXAMPLE 2

[0025] A neonate born at 27 weeks gestational age, weighing 984 grams, and suffering from Hyaline membrane disease was placed in a ventilator and given Exosurf (95cc/kg) at 18 and 30 hrs of age. The patient received an intravenous administration of a neutral (Ph 6.5 - 6.8) 3% L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d., as a continuous infusion. A 6% solution equivalent to 45 mg/kg could have also been administered. The administration was continued until the infant has sufficiently developed to demonstrate adequate blood oxygenation in a normoxic environment, without mechanical or artificial ventilatory support.

[0026] The neonate displayed the following ventilatory requirements at entry and at 28 days:

	Entry	Day 28
Oxygenation index	1.48	0.62
Ventilation rate	920/24hr	223
FiO ₂	1184/24hr	774
Positive end-expiratory pressure	104/24hr	31
Mean airway pressure	208/24hr	56
(Values are summation of area under curve for 24 hour measurements).		

[0027] At 28 days the patient was scored 1.5 for bronchopulmonary dysplasia, 1.0 for retrolental fibroplasia and 0.5 for intraventricular hemorrhage on a 0 to 5 scale (0 being normal, 5 being severe).

EXAMPLE 3

[0028] An 18-year-old hospitalized cystic fibrosis patient received intravenous tobramycin and ceftazidime every eight hours for 6 days. The patient received an intravenous administration of a neutral (pH 6.5 - 6.8) 3% L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d. during continuous infusion. Alternatively, a 6% solution equivalent could have been administered. Although administration occurred during in-patient treatment it could have occurred using home intravenous drug therapy. Administration of the non-cysteine glutathione precursor occurred by independent injection at infusion, but could have taken place by infusion through an indwelling intravenous catheter.

[0029] The following changes in physiological characteristics were recorded at termination of treatment;

SaO ₂	+3.6%
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(continued)

Weight (% increase)	+4.5%
FVC (%predicted)	+15.9%
FEV1 (% predicted)	+14.3%
Bronchoalveolar lavage glutathione	+322%

[0030] The patient with cystic fibrosis also receive an enteral dose of the non-cysteine glutathione precursor equivalent to 15 mg/kg, t.i.d., as a prophylactic treatment during periods free of acute respiratory infection. The enteral dose was given as a capsule, but could have been given as a pill, liquid, or as part of a nutrient containing liquid enteral diet, or as a combination of these delivery methods.

EXAMPLE 4

[0031] A 68-year-old malnourished patient with an acute exacerbation of emphysema is admitted to the respiratory ICU. The patient requires mechanical ventilation and nutritional support. An enteral diet containing 18% protein, 27% CHO, 55 fat is provided at 1.3 times the resting energy expenditure. The diet was supplemented with 15 mg/kg of a non-cysteine glutathione precursor in 250 ml of diet. The patient was successfully weaned from the ventilator and diet on day 8. Lung lavage glutathione levels were taken at admission and on day 7:

	Admission	Day 7
PaCO ₂	6.09	5.15
PaCO ₂ /PAO ₂	31.5	38.4
Ventilation rate (b/m)	31	24
Minute volume (l/m)	16.5	14.2
Glutathione (umol/ml)	95	402

[0032] It is anticipated that a patient with emphysema would receive an enteral dose of a non-cysteine glutathione precursor equivalent to 15 mg/kg, t.i.d., during periods of acute exacerbations, and as a prophylactic treatment during quiescent periods. The enteral dose could be given as a capsule, pill, liquid, or as part of a nutrient containing liquid enteral diet, or as a combination of these delivery methods.

Claims

1. Use of L-2-oxothiazolidine-4-carboxylate for the preparation of a composition for treating a respiratory distress syndrome in a patient suffering from same.
2. The use according to Claim 1 for treating a patient with adult respiratory distress syndrome.
3. The use according to Claim 1 for treating a patient with infant respiratory distress syndrome.
4. Use of L-2-oxothiazolidine-4-carboxylate for the preparation of a composition for treating a patient suffering a disease state or undergoing an acute process which can cause a respiratory distress syndrome.
5. The use according to Claim 4, wherein the disease state is sepsis syndrome.
6. The use according to Claim 4, wherein the disease state or acute process is primary bacterial or viral pneumonia, aspiration of gastric contents, direct chest trauma, prolonged or profound shock, burns, near drowning, fat embolism, blood transfusion, cardiopulmonary bypass, oxygen toxicity or acute haemorrhagic pancreatitis.
7. The use according to any preceding Claim, wherein the composition is administrable parenterally.

8. The use according to any preceding Claim, wherein the composition is administrable enterally.

Patentansprüche

- 5 1. Verwendung von L-2-Oxothiazolidin-4-carboxylat zur Herstellung einer Zusammensetzung zur Behandlung eines Atemnotsyndroms bei einem Patienten, der an demselben leidet.
2. Verwendung nach Anspruch 1 zum Behandeln eines Patienten mit einem Erwachsenen-Atemnotsyndrom.
- 10 3. Verwendung nach Anspruch 1 zum Behandeln eines Patienten mit einem Kinder-Atemnotsyndrom.
4. Verwendung von L-2-Oxothiazolidin-4-carboxylat zur Herstellung einer Zusammensetzung zum Behandeln eines Patienten, der an einem Krankheitszustand leidet oder einen akuten Prozess durchmacht, der ein Atemnotsyndrom verursachen kann.
- 15 5. Verwendung nach Anspruch 4, wobei der Krankheitszustand ein Sepsissyndrom ist.
6. Verwendung nach Anspruch 4, wobei der Krankheitszustand oder der akute Prozess eine primäre bakterielle oder virale Lungenentzündung, eine Aspiration von Mageninhalt, ein direktes Thoraxtrauma, ein verlängerter oder
- 20 profunder Schock, Verbrennungen, ein beinahes Sterben an Lungenödem, eine Fettembolie, eine Bluttransfusion, ein kardiopulmonaler Bypass, eine Sauerstofftoxizität oder eine akute hämorrhagische Pankreatitis ist.
7. Verwendung nach einem der vorhergehenden Ansprüche, wobei die Zusammensetzung parenteral verabreichbar ist.
- 25 8. Verwendung nach einem der vorhergehenden Ansprüche, wobei die Zusammensetzung enteral verabreichbar ist.

Revendications

- 30 1. Utilisation de L-2-oxothiazolidine-4-carboxylate pour la préparation d'une composition pour traiter un syndrome de détresse respiratoire chez un patient souffrant de celui-ci.
2. Utilisation selon la revendication 1 pour traiter un patient ayant un syndrome de détresse respiratoire de l'adulte.
- 35 3. Utilisation selon la revendication 1 pour traiter un patient ayant un syndrome de détresse respiratoire du nourrisson.
4. Utilisation de L-2-oxothiazolidine-4-carboxylate pour la préparation d'une composition pour traiter un patient souffrant d'un état de maladie ou subissant un procédé aigu qui peut provoquer un syndrome de détresse respiratoire.
- 40 5. Utilisation selon la revendication 4, dans laquelle l'état de maladie est un syndrome de septicémie.
6. Utilisation selon la revendication 4, dans laquelle l'état de maladie ou le procédé aigu est une pneumonie virale ou bactérienne primaire, une aspiration des contenus gastriques, un traumatisme de la poitrine direct, un choc prolongé ou profond, des brûlures, une presque noyade, une embolie graisseuse, une transfusion sanguine, une circulation extracorporelle, une toxicité à l'oxygène ou une pancréatite hémorragique aiguë.
- 45 7. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle la composition est administrable parentéralement.
- 50 8. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle la composition est administrable entéralement.